UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/997,722	11/30/2001	David W. Morris	CHIR0024-100(PP23794.001)	3325

55255 7590 10/12/2005

SAGRES DISCOVERY INC.
INTELLECTUAL PROPERTY - R440
P.O. BOX 8097
EMERYVILLE, CA 94662-8097

EXAMINER	
AEDER, SEAN E	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 10/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/997,722	MORRIS ET AL.	
	Examiner	Art Unit	
	Sean E. Aeder, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *1-10,12-17 and 19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11, 18, and 20-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

50

Detailed Action

The Election filed 9/1/05 in response to the Office Action of 6/1/05 is acknowledged and has been entered. Applicant elected group VI with traverse. Applicant further selected SEQ ID NO:174.

The traversal is on the ground(s) that a search and examination of several of the groups identified in the Office Action would not impose a serious burden on the examiner. For example, Applicant asserts that two or more groups of III, IV, V, or VII should be searched together. Applicant also asserts that several of the nucleotide sequences should be considered together. This is not found persuasive.
Groups III, IV, V, and VII are distinct methods which differ at least in objectives, method steps, reagents and/or dosages and/or schedules used, response variables, and criteria for success. Examining these distinct methods would require a burdensome literature search. Further, each nucleotide sequence represents chemically distinct products comprised of a multitude of different nucleotide sequences which are made by materially different methods and have different modes of operation, different functions and different effects. Further, search of each sequence requires an extensive analysis of the art retrieved in a sequence search and will require an in-depth analysis of technical literature. Currently, there are approximately eight different databases that accompany the results of a search of one discrete amino acid or nucleotide sequence and each result set from a particular database must be carefully considered. Hence, the search of all multiple nucleotide sequences in the databases would require extensive

searching and review and would invoke a high burden of search. Furthermore, it is noted that the literature search, particularly relevant in this art, is not coextensive and is very important in evaluating the burden of search. Different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-25 are pending.

Claims 1-10, 12-17, and 19 were withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to a non-elected invention.

Claims 11, 18, and 20-25 are currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11 and 23-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites "...a second unaffected individual...". It is unclear what Applicant means my "unaffected".

Claims 23-25 each recite a percent difference without clearly reciting what the percents indicate. For example, the percent change recited in claim 11 "indicates that the first individual has cancer."

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11, 18, and 20-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re* Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the

invention based on the content of the disclosure. See also *Ex parte* Forman, 230 USPQ 546 (BPAI 1986).

The claims are broadly drawn to a method of diagnosing carcinoma or a propensity for carcinoma by comparing the expression of a nucleotide having 94-98% sequence identity to SEQ ID NO:174 in one sample with another sample from a normal tissue type. The specification discloses that SEQ ID NO:174 is a cancer associated (CA) nucleic acid (page 10 lines 9-12 and table 29, in particular). The specification further discloses that CA nucleic acids are nucleic acids that were identified through use of oncogenic retroviruses, whose sequences insert into the genome of lymphatic tissue resulting in carcinoma (page 3 lines 17-29, in particular). The specification further states that "oncogenes that are identified in one type of cancer such as lymphoma or leukemia have a strong likelihood of being involved in other types of cancers as well..." (page 3 lines 21-24).

However, the specification lacks any working example showing that a nucleotide having 94-98% sequence identity to SEQ ID NO:174 is aberrantly expressed in any cancer type. Further, undue experimentation would be required to determine whether the expression level of nucleotides having 94-98% sequence identity to SEQ ID NO:174 is indicative of any and every carcinoma or indicative of the propensity of an individual for any and every carcinoma. Further, in vitro studies, such as those used by Applicant to identify SEQ ID NO:174, are not highly predictive of cancer in vivo.

Those of skill in the art recognize that in vitro assays and cell culture based assays, such as those used by Applicant to identify SEQ ID NO:174, are generally useful to observe basic physiological and cellular phenomenon such as screening the effects of potential drugs. However, clinical correlations are generally lacking. The greatly increased complexity of the in vivo environment as compared to the very narrowly defined and controlled conditions of an in-vitro assay does not permit a single extrapolation of an in vitro assay to human diagnostic efficacy with any reasonable degree of predictability. In vitro assays cannot easily assess cell-cell interactions that may be important in a particular pathological state. Furthermore, it is well know in the art that cultured cells, over a period of time, lose phenotypic characteristics associated with their normal counterpart cell type. Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts in vivo. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation in vivo. Without this control, cellular metabolism may be more constant in vitro but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p.4, see Major Difference In Vitro). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that,

"Petri dish cancer" is a poor representation of malignancy, with characteristics profoundly different from the human disease. Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not. Yet normal or malignant cells in vivo are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well know in the art that cells in culture exhibit characteristics different from those in vivo and cannot duplicate the complex conditions of the in vivo environment involved in host-tumor and cell-cell interactions.

Those of skill in the art also recognize that the diagnosis of cancer using specific biomarkers has many variables prior to any type of predictive success. Tockman et al (Cancer Research, 1992, 52:2711s-2718s) teaches considerations necessary to bring a cancer biomarker to successful clinical applications. Prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective populations trials (see abstract). Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and ***if validated*** can be used for population screening (page 2713s column 1, in particular). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known

(histology/cytology-confirmed) cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point marker (page 2714, see Biomarker Validation against Acknowledged Disease End Points). Clearly, prior to successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (page 2716s column 2, in particular). In addition, Slamon et al. (Science, 1987, 235:177-182) teach other essential factors that are known to be important in the prognosis of cancer in individual patients such as size of primary tumor, stage of disease at diagnosis, hormonal receptor status, and number of axillary lymph nodes involved with disease (page 178 1st column second paragraph, in particular). Such data are critical for assessing actuarial curves for relapse (figure 3), and for comparing disease-free survival and overall survival to prognostic factors (table 4).

In view of the teachings above, and the lack of guidance or exemplification in the specification, it would not be predictable that the method could be performed as contemplated. Thus, it would require undue experimentation by one of skill in the art to practice the invention as claimed.

Summary

No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean E. Aeder, Ph.D. whose telephone number is 571-272-8787. The examiner can normally be reached on M-F: 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SEA

GARY B. NICKOL, PH.D.
PRIMARY EXAMINER